Assessing risks of polypharmacy involving medications with anticholinergic properties

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Support: KG is funded through a Stroke Association HRH Princess Margaret Clinical Lectureship Award 2017/01. TQ funded through a Joint Stroke Association and Chief Scientist Office Senior Clinical Lectureship. BDJ funded through NHS Research for Scotland (NRS) Career Research Fellowship.

Prior presentations: North American Primary Care Research Group Annual Meeting, Chicago, Nov 2018. Oral presentation.

Word count: 2700

Tables: 2, Figures: 2

Abstract: 249 words

Purpose: Anticholinergic burden (ACB) – cumulative effect of anticholinergic medications – is associated with adverse outcomes in older people but less studied in 'middle-aged' populations. Numerous scales exist to quantify ACB. Aims: to quantify ACB in a large cohort using ten most common anticholinergic scales; to assess association of each scale with adverse outcomes; to assess overlap in populations identified by each scale.

Methods: Longitudinal analysis of UK Biobank community cohort (502,538 participants, baseline age 37-73, median 6 years follow-up). ACB calculated at baseline using ten scales. Linkage to national mortality register and hospital episode statistics. Primary outcome: composite of all cause-mortality or major adverse cardiovascular event (MACE). Secondary outcomes: all-cause mortality, MACE, fall/fracture, hospital admission with dementia/delirium. Cox Proportional hazard models (hazard ratios (HR), 95% confidence intervals (CI)) quantified association between ACB scales and outcomes adjusted for age, sex, socioeconomic status, BMI, smoking, alcohol, physical activity and morbidity count.

Results: Anticholinergic medication use varied from 8.0%-17.6% depending on scale used. Primary outcome: ACB significantly associated with all-cause mortality/MACE using each scale. 'Anticholinergic Drug Scale' most strongly associated (HR 1.12 [CI 1.11-1.14] per one-point increase in score) with mortality/MACE. ACB significantly associated with all secondary outcomes. 'Anticholinergic Effect on Cognition' scale most strongly associated with dementia/delirium (HR 1.45 [CI 1.30-1.61] per one-point increase).

Conclusions: ACB is associated with adverse outcomes in a middle-older aged population. Populations identified and effect size differs between scales. Scale choice influences the population identified as potentially requiring reduction in ACB in clinical practice or intervention trials.

Keywords:

Anticholinergic burden, polypharmacy, multimorbidity, mortality, cardiovascular events

Abbreviations:

AAS	Anticholinergic activity scale (Chew 2008)
AAS-r	Revised anticholinergic activity scale (Ehrt 2010)
ACB	Anticholinergic burden
ACoB	Anticholinergic cognitive burden (Boustani 2008)
ADS	Anticholinergic drug scale (Carnahan 2006
AEC	Anticholinergic effect on cognition(Bishara 2016)
AIS	Anticholinergic impregnation scale (Briet 2017)
ALS	Anticholinergic loading scale (Sittironnarit 2011)
ARS	Anticholinergic risk scale (Rudolph 2008)
CrAS	Clinician-rated anticholinergic scale (Han 2008)
BMI	Body Mass Index
ICD-10	International Classification of Disease, 10^{th} Revision
MACE	Major Adverse Cardiovascular Event
mARS	Modified anticholinergic risk scale (SCPG 2015)

Introduction

Many frequently prescribed medications, for a range of medical conditions, have anticholinergic properties.[1] The use of multiple anticholinergic medications leads to a cumulative effect, referred to as anticholinergic burden (ACB). ACB is associated with adverse outcomes in older people, including mortality, cardiovascular events, falls, and cognitive impairment.[2] Several scales exist to quantify anticholinergic burden,[3-12] however there is no consensus regarding the optimal scale.[13] It is recognized that the population identified as being at risk of adverse outcomes may vary depending on the choice of scale.[14-17] These scales differ in the medications they include and the 'score' they assign to specific medications. Scales for measuring ACB tend to classify medications into four categories from no anticholinergic activity (score = 0) to high anticholinergic activity (score = 3). The scores are calculated by scoring each individual medication a person is taking and then summing these to give an overall score. Validations of these scales vary in study design, age of participants, setting, length of follow-up and methodological quality.[13]

Studies quantifying the impact of ACB have typically focused on patients aged at least 65 years, and often much older. It is not clear if findings from 'high risk' populations, such as nursing home residents, are relevant to the larger population of younger, less frail individuals. People aged <65 years can be affected by multiple chronic conditions (multimorbidity), multiple medications (polypharmacy), and frailty.[18] Understanding how ACB impacts such people is vital if the risks associated with ACB are to be mitigated at a population level.

Using data from UK Biobank, a large community-based cohort of 502,538 participants aged 37-73, this study aimed to quantify anticholinergic burden of participants using the ten most frequently validated anticholinergic scales; assess association of each scale with adverse outcomes previously

linked to ACB; and assess agreement and degree of overlap in the scales for identifying ACB in the same population.

Methods

Study design and participants

UK Biobank is a community-based cohort study of 502,538 participants, recruited between 2006 and 2010 in England, Scotland and Wales. Participants completed a touchscreen questionnaire, interview with a study nurse, and had physical measurements (e.g. height, weight). All participants gave informed consent for data collection, analysis and linkage. This study is part of UK Biobank project 14151 with ethical approval from NHS National Research Ethics Service (16/NW/0274).

Identification of anticholinergic scales

Ten different scales quantifying ACB were identified through systematic literature review[19] (see supplementary appendix): Anticholinergic Drug Scale (ADS),[8] Clinician-rated Anticholinergic Scale (CrAS),[5] Anticholinergic Risk Scale (ARS),[4] Anticholinergic Cognitive Burden (ACoB),[3] Anticholinergic Activity Scale (AAS),[6] revised Anticholinergic Activity Scale (AAS-r),[7] Anticholinergic Loading Scale (ALS),[9] Modified Anticholinergic Risk Scale (m-ARS),[12] Anticholinergic Effect on Cognition (AEC),[10] Anticholinergic Impregnation Scale (AIS).[11]

Baseline variables

All participants reported medications taken at the time of recruitment during an interview with a trained study nurse. Participants were asked to name all “regular medications” taken, excluding “short-term medications” (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100075). Specific data on dose, formulation and duration were not collected. The British National Formulary was used to

identify generic and branded names for each medication.[20] We calculated each participant's ACB at baseline using each of the identified scales. Weightings for each medication (0-3) were taken from the published description of each scale, and then summed to give a numerical value for each scale.

The following baseline variables were used in adjusted analyses: age; sex; socioeconomic status (Townsend score derived from participant postcodes); body mass index (BMI) (categorised into <18.5, 18.5-24.9, 25.0-29.9, ≥30.0); smoking (current, ex-, and non-smoker); alcohol frequency (never/special occasions only; one to three times/month; one to four times/week; daily/almost daily) and physical activity (classified into levels of physical activity in the last four weeks: none; low (light 'DIY' activity only); medium (heavy DIY and/or walking for pleasure and/or other exercises); and high (strenuous sports). Participants also reported morbidities at the baseline assessment. The morbidities described in this paper were taken from a list of 43 morbidities originally established for a large epidemiological study in Scotland and subsequently amended for UK Biobank.[21,22] Number of morbidities reported were summed to give a morbidity count.

Outcomes

All outcomes were identified prospectively using data linkage. Baseline data were linked to national mortality records and hospital episode statistics (HES). HES outcomes were identified using ICD-10 diagnostic codes. Median follow-up 74.7 months (interquartile range 66.1 to 81.7).

Primary outcome:

- Composite outcome: all-cause mortality or Major Adverse Cardiovascular Event (MACE) (defined as non-fatal MI (I21), non-fatal stroke (I63, I64), or cardiovascular death (primary cause of death coded "I")

Secondary outcomes

- All-cause mortality
- MACE
- Hospital admission with fall (W0, W1) or fracture (S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T05)
- Hospital admission with dementia or delirium (F00, F01, F02, F03, F05) (analysis limited to participants without a dementia diagnosis at baseline)

Statistical analysis

All analyses were pre-specified prior to inspection of the data in keeping with STROBE guidelines.[23]

Baseline descriptive analysis

We divided the cohort into participants taking any anticholinergic medication at baseline according to any of the ten scales, and those taking no anticholinergic medication. Age, sex, socioeconomic status, smoking, BMI, alcohol frequency, morbidity count, and number of medications were summarised for each group.

Time-to-event analyses – main analysis

We used Cox proportional hazard models to assess the risk of each outcome for baseline values of each of the anticholinergic scales. We examined log-log survival curves to assess the proportional hazards assumption for each variable. Cause specific-models were used to account for competing risks.[24] Each outcome was modelled using time to first event.

For the main analysis, hazard ratios with 95% confidence intervals were calculated for a one-point increase in ACB for each scale. We excluded participants with missing data for one or more covariates. Each scale was modelled separately using three different models:

- Model 1: Adjusted for age, sex, and socioeconomic status (n=501,992, 0.1% missing)
- Model 2: Model 1 plus adjustment for BMI, smoking, alcohol frequency and physical activity (n=487,697, 3% missing)
- Model 3: Model 2 plus adjustment for morbidity count (n=483,182, 3% missing)

Contribution of the anticholinergic scale was assessed by calculating the proportion of explainable variance explained by the scale. The predictive accuracy of model 3 was assessed using Harrell's C-statistic with ten-fold internal cross-validation. The C-statistic of a base model (including all covariates except the anticholinergic scale) was calculated for comparison.

Time-to-event analyses – sensitivity analyses

We performed three pre-specified sensitivity analyses to assess potential sources of bias:

1. Excluding events occurring in the first 12 months of follow-up (limits bias from reverse causality)
2. Follow-up truncated at 24 months, with participants censored at first event or 24 months follow-up, whichever happened first (to limit bias from unmeasured fluctuations in ACB over the full follow up period)
3. Model adjusted for all covariates of model 2 plus hypertension, coronary heart disease, diabetes, stroke/transient ischaemic attack, and heart failure at baseline. For primary outcome (cardiovascular event or death), all-cause mortality, and MACE

Assessment of overlap of anticholinergic scales

A Venn diagram was constructed using the four most frequently validated scales (ARS, ADS, CrAS, ACB [13]) to assess the level of overlap in participants identified scoring 1 or more in these scales.[3-5,8,13]

Results

Baseline characteristics

Sociodemographic characteristics are shown in Table 1. Participants taking anticholinergic medication were significantly older, more likely to be female, to be current or ex-smokers, to report infrequent or no alcohol intake, and to have low physical activity. Median morbidity count was higher in those with higher ACB, as was median number of medications.

ACB in UK Biobank participants

Figure 1 shows the ACB in UK Biobank participants using each of the ten scales. There was variation between scales in the number of people identified at all levels. The ALS identified the highest number of people as taking anticholinergic medication (n=88,409, 17.6%). The ARS identified the fewest (n=40,298, 8.0%).

Outcomes

Primary outcome: MACE or Death (composite outcome)

A total of 16,375 (3%) participants experienced either non-fatal MI, stroke, or died within the follow-up period. Higher ACB was significantly associated with a higher risk of the primary outcome for all scales (table 2). The effect size associated with ACB was attenuated when adjusting for potential confounders (supplementary appendix). In the fully adjusted model (adjusted age, sex, socioeconomic status, BMI, smoking, alcohol, physical activity and morbidity count) hazard ratios per one-point increase in anticholinergic scale ranged from 1.05 (95% CI 1.03 to 1.07) for ARS to 1.12 (1.11 to 1.14) for ADS.

Sensitivity analyses one (excluding events in the first year) and three (controlling for cardiovascular comorbidity) showed similar results to the main analysis. In sensitivity analysis two (truncated at 2 years follow-up) ARS was not significantly associated with MACE or death.

Secondary outcomes

For each anticholinergic scale, hazard ratios from the fully adjusted model for each of the secondary outcomes are shown in table 2.

When considering all-cause mortality and MACE separately, results were similar to the composite primary outcome.

Each scale was significantly associated with risk of fall/fracture. But the predictive accuracy was lower than for other outcomes (e.g. C-statistic 0.626 with ADS, see supplementary appendix).

Two hundred and ten participants (not reporting dementia at baseline) had a hospital admission with dementia or delirium during follow-up. Each scale was significantly associated with increased risk (table 2). The AEC score, which was designed to assess risk of neurocognitive complications, showed the greatest effect size for this outcome (HR 1.45, 95% CI 1.30 to 1.61). Models including AEC had the highest predictive accuracy for dementia/delirium compared to the base model (C-statistic 0.832 and 0.806, respectively). HRs for ARS and AAS-r scales were no longer significant after excluding admissions in the first year. Truncating follow-up at 2 years, AAS-r did not show significant effect sizes (supplementary appendix).

Overlap of populations identified by scales

To illustrate the degree of overlap in populations identified as at risk by different scales, participants scoring ≥1 on any of the four most validated scales (ADS, CrAS, ARS and ACB)[3-5,8] are included in Figure 2. Only 23% of these participants scored ≥1 on all four scales.

Discussion

Summary of findings

We demonstrate that there is considerable variability between scales in the proportion of participants identified as taking anticholinergic medication and the quantification of ACB. Regarding the four most validated scales,[3-5,8] less than one in four of those scoring ≥1 in any scale were identified by all four scales. Despite this, a modest association between anticholinergic medication use and cardiovascular events, mortality, admission due to fall/fracture or dementia/delirium was seen across all scales after adjusting for multiple clinical and sociodemographic factors. Small effect sizes of this kind may still be important at the population level, especially when there is no proven intervention that halts or delays cognitive decline, one of the important adverse effects. The association between ACB and outcomes has biological plausibility. Our results seem robust, as associations remained consistent when corrected for potential confounders and across several pre-specified sensitivity analyses. Effect sizes for AEC and AIS, which were developed to predict neurocognitive outcomes, were higher for dementia/delirium, however confidence intervals overlapped with the other scales. While there is a consistent association between ACB and risk of adverse outcomes, regardless of scale used, the populations identified as being at risk vary considerably depending on which scale is used. This has important implications if ACB is to be assessed in clinical practice and interventions designed to reduce its impact.

Strengths and limitations

The UK Biobank cohort is larger than any previous cohort assessing ACB and includes data covering a wide range of sociodemographic and lifestyle characteristics. Follow-up through linkage to national HES and mortality registers limits recall bias in outcome assessment, but relies on these events resulting in an inpatient episode and being accurately coded. While this is unlikely to impact our identification of MACE, mortality and fractures, other outcomes such as falls and dementia/delirium

may lack sensitivity.[25] While the length of follow-up is an advantage, ACB and the extent of multimorbidity may change over time. These changes are not captured by modelling only baseline values. We conducted a sensitivity analysis, truncating follow-up at two years, to limit bias caused by unmeasured fluctuations in ACB or multimorbidity over the follow-up period. However, such an analysis may only partially mitigate potential bias from unmeasured changes over time. All medication and morbidity variables were defined by self-report, which is a potential source of bias. UK Biobank data are not currently linked to primary care or prescribing databases that could validate medication use or diagnoses. However participants were supported by a study nurse in providing accurate medical and drug history, and limitations of self-report would be expected to impact each scale similarly. Finally, we did not have information on dosage or duration of anticholinergic medication taken. The included scales do not specify medication dose, however this meant we were unable to include alterative scales such as the Drug Burden Index, which includes a sub-scale assessing ACB.[26] Duration of medication usage is also likely to be an important factor in risk of adverse outcomes, and we were not able to measure this in our study.

Our findings indicate association only. A causal relationship between ACB and adverse outcomes is not proven. Our findings, like any observational study, are susceptible to residual confounding. Assessing adverse consequences from medication use is particularly susceptible to confounding by indication (the indicating illness, rather than medication, is the causative factor in adverse outcomes).[27] We attempted to limit this by adjusting for morbidity count as a measure of chronic disease burden. Results remained significant, although hazard ratios were attenuated. We also conducted a sensitivity analysis for cardiovascular outcomes adjusting for a range of cardio-metabolic comorbidities, with similar results. However, these analyses cannot rule out residual confounding.

Context and implications

Recommendations to reduce ACB are starting to be included in clinical guidelines (e.g. for dementia or polypharmacy).[28,29] Our findings indicate the number of people identified as being 'at risk' will vary depending on measures used (ALS identified more than twice as many people as ARS) and different scales will identify different people. ARS and ACoB had the highest effect size for the primary outcome, although point estimates for AEC and AIS were higher for neurocognitive outcomes. Rather than identifying an optimal scale, our findings highlight pitfalls and implications which should be considered when attempting to identify and reduce ACB. Simplicity and usability of scales is also relevant to clinical use. The importance of classes of medications, compared to high or low scores, should also be explored.[30]

There is a need to explore the impact of reducing ACB at a population level, as existing interventions' focus is limited to frail older people.[31,32] The average age of UK Biobank participants is younger than previous cohorts validating these scales (mean ages generally >70 years, many conducted in nursing homes or palliative care settings). UK Biobank is more affluent and less multimorbid than the UK average.[33] While this limits accurate inference regarding prevalence of ACB in the general population, relationships between exposures and outcomes remain valid. However, the effect sizes seen in our study were modest, and the impact of reducing ACB at an individual level is not clear. Furthermore, residual confounding – particularly confounding by indication – cannot be excluded as an explanation for the associations seen. Our findings that ACB is associated with various adverse outcomes, in a younger and relatively healthier population than previously studied, highlight that there may be value in interventions to reduce ACB at a population level as the absolute numbers of people potentially at risk is high. Developing such an intervention would require investigation of barriers and facilitators to optimising anticholinergic prescribing at a patient, professional and

organisational level. However, there is also a need to understand what factors increase susceptibility to adverse effects of ACB (e.g. older age, frailty, etc.), and these should be identified.

Conclusion

In a middle-older aged population of >500,000 people we demonstrate levels of anticholinergic prescribing ranging from 7.0% to 17.6% depending on the scale used. There was an association of anticholinergic medication use with cardiovascular events, mortality, falls, fractures and dementia/delirium admissions irrespective of scale used. This was true after adjusting for sociodemographic factors and morbidities**.** However, different populations will be identified depending on the scale used. These findings should inform their use in clinical practice and in decision making in future intervention trials.

Acknowledgements: The authors declare no conflicts of interest.

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Acquisition, analysis, or interpretation of data: PH, KG, BDJ, BN, DL, RLS, PKM, FSM

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Statistical analysis: PH, DL

Obtaining funding: KG is funded through a Stroke Association HRH Princess Margaret Clinical Lectureship Award 2017/01. TQ funded through a Joint Stroke Association and Chief Scientist Office Senior Clinical Lectureship. BDJ funded through NHS Research for Scotland (NRS) Career Research Fellowship.

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Table 1: Baseline characteristics		
Variable	Score = 0 on all scales N = 367,319	Score 1 or more on any scale N = 135,321
Age (median, IQR)	57 (IQR: 49-62)	60 (IQR: 53-65)
Missing	0	0
Sex (%)		
Female	198,346 (54%)	75,120 (55.5%)
Male	168,973 (46%	60,201 (44.5%)
Missing	0	0
Townsend score quintile (socioeconomic status) (%)		
1 (least deprived)	77,293 (21.1.%)	23,394 (17.3%)
2	75,738 (20.6%)	24,381 (18.0%)
3	74,334 (20.3%)	26,078 (19.3%)
4	72,916 (19.9%)	27,479 (20.3%)
5 (most deprived)	66,602 (18.2%)	33,798 (25.0%)
Missing	436	191
BMI category (%)		
<18.5	1975 (0.5%)	651 (0.5%)
18.5-24.9	127,500 (35%)	29,887 (22.5%)
25.0-29.9	179,715 (43.8%)	54,552 (41.1%)
≥30	74,969 (20.6%)	47,491 (35.8%)
Missing	3,080	2,740

Smoking status (%)		
Never	208,977 (57.2%)	64,624 (48.1%)
Previous	120,154 (32.9%)	52,944 (39.4%)
Current	36,210 (9.9%)	16,779 (12.5%)
Missing	1,978	974
Alcohol frequency (%)		
Never/special occasions	61,230 (16.7%)	37,460 (27.8%)
1-3 times per month	39,987 (10.9%)	15.886 (11.0%)
1-4 times per week	187,445 (51.2%)	57,339 (42.5%)
Daily/almost daily	77,572 (21.2%)	24,218 (18.0%)
Missing	1,085	418
Physical activity (%)		
High	43,279 (11.9%)	6,798 (5.1%)
Medium	290,383 (80.0)	103,221 (77.9%)
Low	11,330 (3.1%)	7,613 (5.7%)
None	17,983 (5.0%)	14,875 (11.2%)
Missing	4,344	2,814
Number of comorbid conditions (median, IQR)	1 (IQR: 0-1)	2 (IQR: 1-3)
Missing	1,173	672
Total number of regular medications (median, IQR)	1 (IQR: 0-2)	4 (IQR: 3-7)
Missing	862	Missing

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Table 2: Hazard ratio (and 95% confidence interval) of anticholinergic scales with outcomes.					
scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
CrAS	1.05 (1.03 to 1.07)	1.05 (1.04 to 1.07)	1.03 (1.0 to 1.06)	1.09 (1.06 to 1.11)	1.23 (1.1 to 1.36)
ARS	1.05 (1.03 to 1.08)	1.06 (1.04 to 1.08)	1.01 (0.97 to 1.05)	1.06 (1.03 to 1.10)	1.23 (1.07 to 1.40)
AAS-r	1.06 (1.04 to 1.08)	1.07 (1.05 to 1.08)	1.07 (1.04 to 1.09)	1.09 (1.06 to 1.12)	1.14 (1.02 to 1.28)
ALS	1.06 (1.04 to 1.08)	1.07 (1.05 to 1.08)	1.04 (1.01 to 1.07)	1.1 (1.07 to 1.13)	1.26 (1.14 to 1.41)
AAS	1.06 (1.05 to 1.08)	1.07 (1.05 to 1.09)	1.07 (1.05 to 1.10)	1.09 (1.06 to 1.12)	1.24 (1.11 to 1.37)
AEC	1.07 (1.05 to 1.10)	1.08 (1.06 to 1.10)	1.04 (1.00 to 1.08)	1.12 (1.09 to 1.16)	1.45 (1.30 to 1.61)
m-ARS	1.07 (1.06 to 1.09)	1.08 (1.06 to 1.10)	1.02 (0.99 to 1.06)	1.08 (1.05 to 1.12)	1.27 (1.13 to 1.43)
AIS	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.11)	1.04 (1.01 to 1.08)	1.14 (1.1 to 1.17)	1.38 (1.24 to 1.54)
ACoB	1.12 (1.10 to 1.14)	1.13 (1.11 to 1.15)	1.17 (1.14 to 1.20)	1.11 (1.08 to 1.14)	1.26 (1.14 to 1.40)
ADS	1.12 (1.11 to 1.14)	1.13 (1.12 to 1.15)	1.15 (1.12 to 1.17)	1.13 (1.10 to 1.16)	1.29 (1.16 to 1.42)
Results from model 3: Adjusted for age, sex, socioeconomic status, BMI, smoking, alcohol, physical activity, and morbidity count.					

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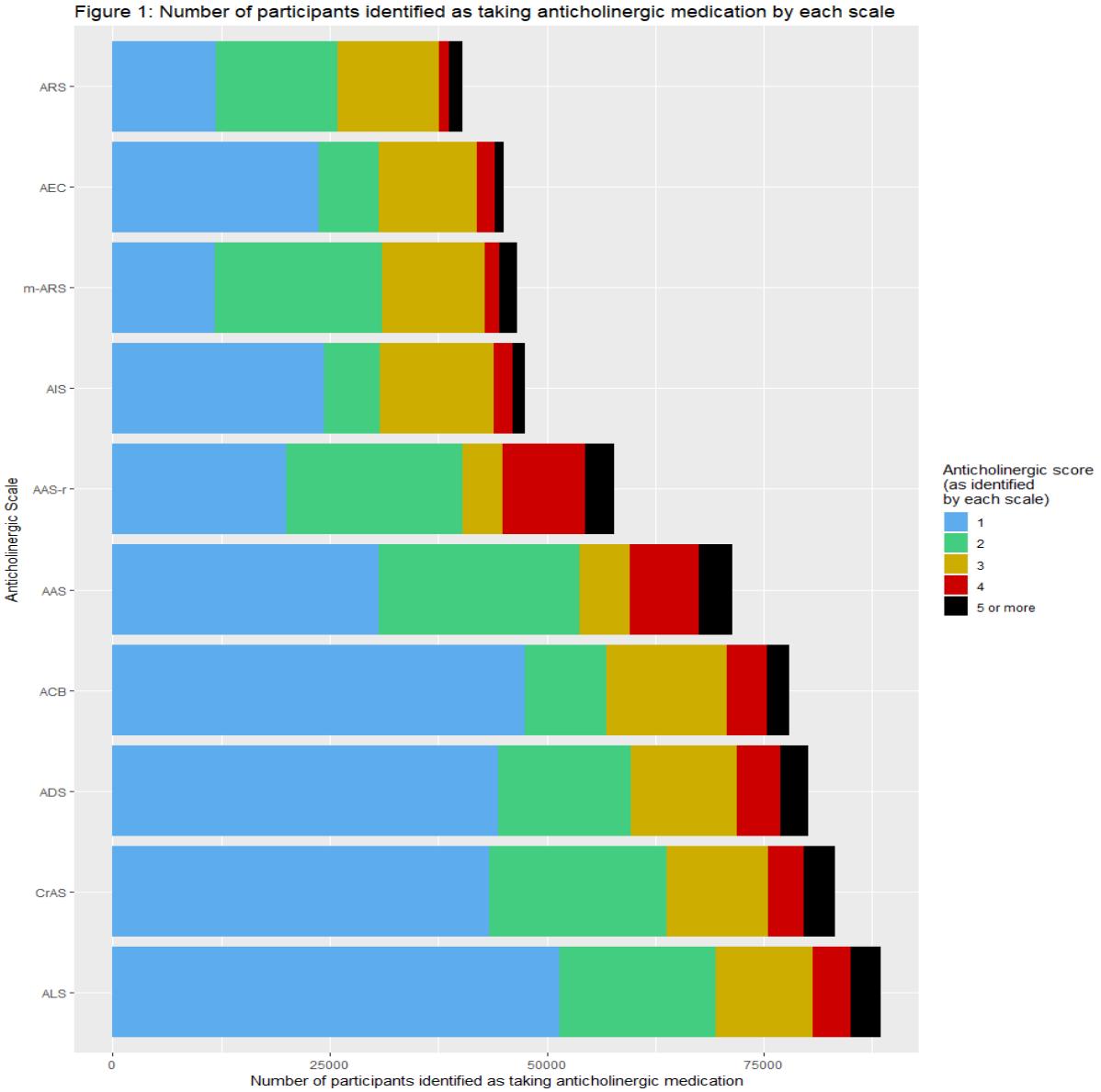
Figure 1: Number of participants identified as taking anticholinergic medication by each scale



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ARS	Anticholinergic risk scale (Rudolph 2008)	49 included medications
AEC	Anticholinergic effect on cognition(Bishara 2016)	122 included medications
mARS	Modified anticholinergic risk scale (SCPG 2015)	61 included medications
AIS	Anticholinergic impregnation scale (Briet 2017)	128 included medications
AAS-r	Revised anticholinergic activity scale (Ehrt 2010)	99 included medications
AAS	Anticholinergic activity scale (Chew 2008)	107 included medications
ACoB	Anticholinergic cognitive burden (Boustani 2008)	88 included medications
ADS	Anticholinergic drug scale (Carnahan 2006)	117 included medications
CrAS	Clinician-rated anticholinergic scale (Han 2008)	60 included medications
ALS	Anticholinergic loading scale (Sittironnarit 2011)	49 included medications

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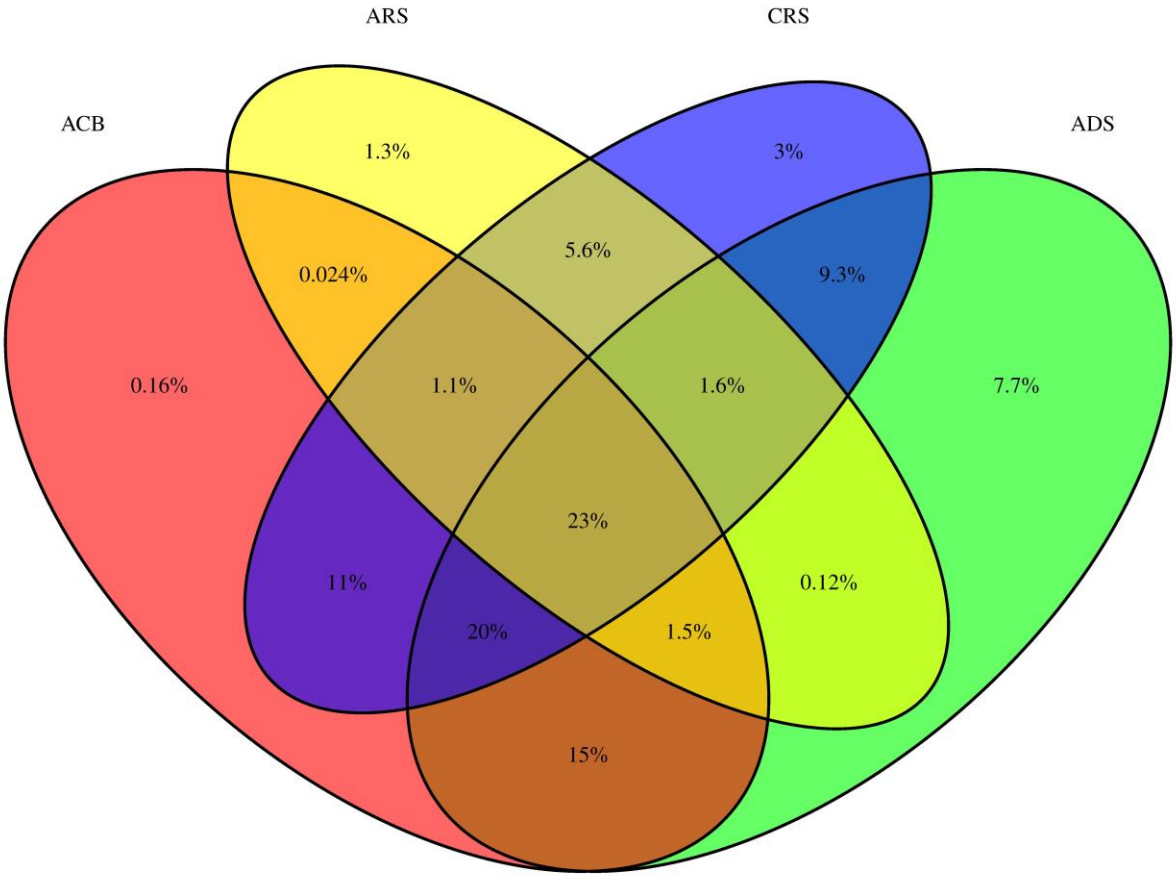
410 Figure 2: Venn diagram of participants scoring ‘1 or more’ on any of the four most validated scales



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Supplementary appendix

Contents

Main analysis

Hazard ratios per one-point increase in scale

Model 1 - Adjusted for age, sex, and socioeconomic status

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.21 (1.19 to 1.23)	1.22 (1.2 to 1.24)	1.21 (1.17 to 1.25)	1.15 (1.12 to 1.19)	1.38 (1.23 to 1.55)
CrAS	1.21 (1.2 to 1.23)	1.22 (1.2 to 1.24)	1.25 (1.22 to 1.27)	1.17 (1.14 to 1.19)	1.36 (1.24 to 1.49)
AAS-r	1.22 (1.2 to 1.23)	1.22 (1.21 to 1.24)	1.27 (1.25 to 1.3)	1.17 (1.15 to 1.2)	1.28 (1.17 to 1.41)
AAS	1.23 (1.22 to 1.25)	1.24 (1.22 to 1.25)	1.29 (1.27 to 1.32)	1.17 (1.15 to 1.2)	1.39 (1.28 to 1.51)
m-ARS	1.24 (1.22 to 1.25)	1.24 (1.23 to 1.26)	1.23 (1.2 to 1.27)	1.17 (1.14 to 1.2)	1.41 (1.28 to 1.56)
ALS	1.24 (1.23 to 1.26)	1.25 (1.23 to 1.26)	1.28 (1.25 to 1.31)	1.18 (1.16 to 1.21)	1.41 (1.29 to 1.53)
AIS	1.26 (1.24 to 1.28)	1.27 (1.25 to 1.29)	1.28 (1.24 to 1.31)	1.24 (1.21 to 1.27)	1.51 (1.38 to 1.66)
AEC	1.26 (1.24 to 1.29)	1.27 (1.25 to 1.3)	1.28 (1.25 to 1.32)	1.23 (1.2 to 1.27)	1.61 (1.47 to 1.77)
ACOB	1.28 (1.27 to 1.3)	1.29 (1.28 to 1.31)	1.38 (1.35 to 1.4)	1.21 (1.18 to 1.24)	1.43 (1.32 to 1.55)
ADS	1.29 (1.28 to 1.31)	1.3 (1.29 to 1.32)	1.37 (1.34 to 1.39)	1.22 (1.2 to 1.25)	1.43 (1.32 to 1.55)

Model 2 - adjusted for age, sex, socioeconomic status, BMI, smoking, alchohol and phyiscal activity

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.14 (1.12 to 1.16)	1.14 (1.12 to 1.17)	1.11 (1.08 to 1.15)	1.12 (1.08 to 1.16)	1.34 (1.18 to 1.52)
CrAS	1.14 (1.12 to 1.16)	1.15 (1.13 to 1.16)	1.14 (1.11 to 1.17)	1.14 (1.12 to 1.17)	1.34 (1.21 to 1.47)
AAS-r	1.14 (1.13 to 1.16)	1.15 (1.13 to 1.17)	1.17 (1.14 to 1.2)	1.14 (1.12 to 1.17)	1.26 (1.14 to 1.4)
AAS	1.15 (1.14 to 1.17)	1.16 (1.15 to 1.18)	1.19 (1.16 to 1.21)	1.15 (1.12 to 1.17)	1.35 (1.23 to 1.48)
ALS	1.16 (1.14 to 1.18)	1.17 (1.15 to 1.19)	1.17 (1.14 to 1.2)	1.16 (1.13 to 1.19)	1.38 (1.25 to 1.52)
m-ARS	1.16 (1.14 to 1.18)	1.17 (1.15 to 1.19)	1.13 (1.1 to 1.17)	1.14 (1.11 to 1.17)	1.38 (1.24 to 1.54)
AEC	1.17 (1.15 to 1.19)	1.18 (1.16 to 1.2)	1.16 (1.12 to 1.2)	1.19 (1.15 to 1.23)	1.57 (1.42 to 1.73)
AIS	1.18 (1.16 to 1.2)	1.19 (1.17 to 1.21)	1.16 (1.12 to 1.2)	1.2 (1.17 to 1.23)	1.5 (1.35 to 1.66)
ACOB	1.21 (1.19 to 1.22)	1.22 (1.2 to 1.24)	1.27 (1.24 to 1.3)	1.17 (1.15 to 1.2)	1.38 (1.26 to 1.51)
ADS	1.21 (1.2 to 1.23)	1.22 (1.21 to 1.24)	1.25 (1.23 to 1.28)	1.19 (1.16 to 1.21)	1.4 (1.28 to 1.53)

Model 3 - adjuted for age, sex, socioeconomic status, BMI, smoking, alchohol, physical activity and number of long-term conditions

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
CrAS	1.05 (1.03 to 1.07)	1.05 (1.04 to 1.07)	1.03 (1 to 1.06)	1.09 (1.06 to 1.11)	1.23 (1.1 to 1.36)
ARS	1.05 (1.03 to 1.08)	1.06 (1.04 to 1.08)	1.01 (0.97 to 1.05)	1.06 (1.03 to 1.1)	1.23 (1.07 to 1.4)
AAS-r	1.06 (1.04 to 1.08)	1.07 (1.05 to 1.08)	1.07 (1.04 to 1.09)	1.09 (1.06 to 1.12)	1.14 (1.02 to 1.28)
ALS	1.06 (1.04 to 1.08)	1.07 (1.05 to 1.08)	1.04 (1.01 to 1.07)	1.1 (1.07 to 1.13)	1.26 (1.14 to 1.41)
AAS	1.06 (1.05 to 1.08)	1.07 (1.05 to 1.09)	1.07 (1.05 to 1.1)	1.09 (1.06 to 1.12)	1.24 (1.11 to 1.37)
AEC	1.07 (1.05 to 1.1)	1.08 (1.06 to 1.1)	1.04 (1 to 1.08)	1.12 (1.09 to 1.16)	1.45 (1.3 to 1.61)
m-ARS	1.07 (1.06 to 1.09)	1.08 (1.06 to 1.1)	1.02 (0.99 to 1.06)	1.08 (1.05 to 1.12)	1.27 (1.13 to 1.43)
AIS	1.08 (1.06 to 1.1)	1.09 (1.07 to 1.11)	1.04 (1.01 to 1.08)	1.14 (1.1 to 1.17)	1.38 (1.24 to 1.54)
ACOB	1.12 (1.1 to 1.14)	1.13 (1.11 to 1.15)	1.17 (1.14 to 1.2)	1.11 (1.08 to 1.14)	1.26 (1.14 to 1.4)
ADS	1.12 (1.11 to 1.14)	1.13 (1.12 to 1.15)	1.15 (1.12 to 1.17)	1.13 (1.1 to 1.16)	1.29 (1.16 to 1.42)

Predictive accuracy of fully adjusted model

The predictive accuracy of model 3 was assessed using Harrell's C-statistic with ten-fold internal cross-validation. C-statistic is an extension of the area under the curve for time-to-event data. A value of 1 indicates perfect prediction and a value of 0.5 no better than chance. The C-statistic of a base model (including all covariates except the anticholinergic scale) was calculated for comparison.

C statistics for model 3

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
Base model (add covariates minus anticholinergic score)	0.737	0.741	0.757	0.623	0.820
CrAS	0.737	0.741	0.757	0.624	0.822
ARS	0.737	0.741	0.757	0.624	0.822
AAS-r	0.737	0.741	0.757	0.625	0.822
ALS	0.737	0.741	0.757	0.625	0.822
AAS	0.737	0.741	0.757	0.625	0.822
AEC	0.737	0.741	0.757	0.625	0.823
m-ARS	0.737	0.741	0.757	0.624	0.823
AIS	0.737	0.742	0.757	0.625	0.823
ACOB	0.738	0.743	0.758	0.625	0.822
ADS	0.738	0.742	0.758	0.626	0.822

Sensitivity analysis 1: Excluding events occurring in the first 12 months of follow-up (limits bias from reverse causality)

Hazard ratios per one-point increase in scale

Model 1 - Adjusted for age, sex, and socioeconomic status

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.21 (1.19 to 1.23)	1.21 (1.19 to 1.24)	1.22 (1.17 to 1.26)	1.17 (1.13 to 1.22)	1.28 (1.1 to 1.49)
CrAS	1.21 (1.2 to 1.23)	1.22 (1.2 to 1.23)	1.26 (1.23 to 1.29)	1.18 (1.15 to 1.21)	1.28 (1.14 to 1.44)
AAS-r	1.22 (1.2 to 1.23)	1.22 (1.2 to 1.24)	1.29 (1.26 to 1.32)	1.18 (1.15 to 1.21)	1.26 (1.13 to 1.41)
AAS	1.23 (1.21 to 1.24)	1.23 (1.22 to 1.25)	1.31 (1.28 to 1.34)	1.18 (1.15 to 1.21)	1.34 (1.22 to 1.49)
ALS	1.24 (1.22 to 1.26)	1.24 (1.23 to 1.26)	1.3 (1.27 to 1.33)	1.2 (1.17 to 1.24)	1.33 (1.2 to 1.49)
m-ARS	1.24 (1.22 to 1.26)	1.24 (1.22 to 1.26)	1.24 (1.2 to 1.28)	1.19 (1.15 to 1.23)	1.32 (1.16 to 1.5)
AEC	1.26 (1.24 to 1.28)	1.27 (1.24 to 1.29)	1.3 (1.26 to 1.35)	1.25 (1.2 to 1.29)	1.5 (1.33 to 1.69)
AIS	1.26 (1.24 to 1.28)	1.27 (1.25 to 1.29)	1.29 (1.26 to 1.33)	1.24 (1.2 to 1.28)	1.47 (1.31 to 1.65)
ACOB	1.28 (1.26 to 1.3)	1.29 (1.27 to 1.3)	1.4 (1.37 to 1.43)	1.22 (1.19 to 1.26)	1.34 (1.2 to 1.49)
ADS	1.29 (1.27 to 1.3)	1.3 (1.28 to 1.31)	1.39 (1.36 to 1.42)	1.24 (1.21 to 1.27)	1.36 (1.23 to 1.51)

Model 2 - adjusted for age, sex, socioeconomic status, BMI, smoking, alchohol and phyiscal activity

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.14 (1.12 to 1.16)	1.14 (1.12 to 1.17)	1.12 (1.08 to 1.17)	1.14 (1.1 to 1.19)	1.24 (1.05 to 1.46)
CrAS	1.14 (1.12 to 1.16)	1.15 (1.13 to 1.16)	1.16 (1.13 to 1.19)	1.16 (1.12 to 1.19)	1.27 (1.12 to 1.43)
AAS-r	1.14 (1.13 to 1.16)	1.15 (1.13 to 1.16)	1.19 (1.16 to 1.22)	1.15 (1.12 to 1.19)	1.24 (1.1 to 1.4)
AAS	1.15 (1.14 to 1.17)	1.16 (1.14 to 1.17)	1.21 (1.18 to 1.24)	1.16 (1.13 to 1.2)	1.31 (1.17 to 1.47)
ALS	1.16 (1.14 to 1.18)	1.17 (1.15 to 1.18)	1.19 (1.15 to 1.22)	1.19 (1.15 to 1.22)	1.31 (1.16 to 1.48)
m-ARS	1.16 (1.14 to 1.18)	1.17 (1.15 to 1.19)	1.14 (1.1 to 1.18)	1.16 (1.12 to 1.2)	1.29 (1.13 to 1.49)
AEC	1.17 (1.15 to 1.19)	1.17 (1.15 to 1.2)	1.18 (1.14 to 1.23)	1.21 (1.16 to 1.26)	1.47 (1.29 to 1.68)
AIS	1.18 (1.16 to 1.2)	1.18 (1.16 to 1.2)	1.18 (1.14 to 1.22)	1.21 (1.17 to 1.25)	1.47 (1.3 to 1.66)
ACOB	1.21 (1.19 to 1.22)	1.21 (1.2 to 1.23)	1.29 (1.26 to 1.32)	1.19 (1.15 to 1.22)	1.29 (1.14 to 1.45)
ADS	1.21 (1.19 to 1.23)	1.22 (1.2 to 1.24)	1.28 (1.25 to 1.31)	1.21 (1.17 to 1.24)	1.32 (1.18 to 1.48)

Model 3 - adjuted for age, sex, socioeconomic status, BMI, smoking, alchohol, physical activity and number of long-term conditions

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
CrAS	1.06 (1.04 to 1.07)	1.06 (1.04 to 1.07)	1.04 (1.01 to 1.08)	1.1 (1.06 to 1.14)	1.15 (1 to 1.31)
ARS	1.06 (1.04 to 1.08)	1.06 (1.04 to 1.08)	1.02 (0.98 to 1.06)	1.09 (1.04 to 1.13)	1.12 (0.94 to 1.33)
AAS-r	1.06 (1.05 to 1.08)	1.06 (1.05 to 1.08)	1.09 (1.06 to 1.12)	1.1 (1.06 to 1.13)	1.11 (0.97 to 1.27)
AAS	1.07 (1.05 to 1.08)	1.07 (1.05 to 1.09)	1.09 (1.06 to 1.13)	1.11 (1.07 to 1.14)	1.18 (1.04 to 1.34)
ALS	1.07 (1.05 to 1.08)	1.07 (1.05 to 1.09)	1.06 (1.03 to 1.09)	1.12 (1.09 to 1.16)	1.18 (1.03 to 1.35)
AEC	1.08 (1.05 to 1.1)	1.08 (1.06 to 1.1)	1.06 (1.02 to 1.1)	1.14 (1.1 to 1.19)	1.34 (1.16 to 1.54)
m-ARS	1.08 (1.06 to 1.1)	1.08 (1.06 to 1.1)	1.03 (0.99 to 1.07)	1.1 (1.06 to 1.14)	1.18 (1.01 to 1.36)
AIS	1.09 (1.07 to 1.11)	1.09 (1.07 to 1.11)	1.06 (1.02 to 1.1)	1.14 (1.1 to 1.19)	1.35 (1.18 to 1.54)
ACOB	1.12 (1.1 to 1.14)	1.13 (1.11 to 1.14)	1.19 (1.16 to 1.22)	1.13 (1.09 to 1.16)	1.15 (1 to 1.32)
ADS	1.13 (1.11 to 1.14)	1.13 (1.11 to 1.15)	1.17 (1.14 to 1.2)	1.15 (1.11 to 1.18)	1.19 (1.05 to 1.35)

Sensitivity analysis 2: Follow-up truncated at 24 months, with participants censored at first event or 24 months follow-up, whichever happened first (to limit bias from unmeasured change in anticholinergic burden)

Hazard ratios per one-point increase in scale

Model 1 - Adjusted for age, sex, and socioeconomic status

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.23 (1.18 to 1.27)	1.23 (1.18 to 1.28)	1.19 (1.13 to 1.25)	1.13 (1.09 to 1.18)	1.38 (1.18 to 1.61)
CrAS	1.24 (1.21 to 1.27)	1.26 (1.23 to 1.3)	1.21 (1.16 to 1.25)	1.15 (1.12 to 1.18)	1.35 (1.19 to 1.52)
m-ARS	1.24 (1.21 to 1.28)	1.26 (1.21 to 1.31)	1.2 (1.15 to 1.26)	1.15 (1.12 to 1.19)	1.42 (1.24 to 1.62)
AAS-r	1.25 (1.22 to 1.28)	1.28 (1.24 to 1.31)	1.24 (1.2 to 1.28)	1.17 (1.14 to 1.2)	1.27 (1.12 to 1.44)
AAS	1.26 (1.23 to 1.29)	1.3 (1.26 to 1.33)	1.24 (1.2 to 1.29)	1.16 (1.13 to 1.19)	1.39 (1.24 to 1.55)
ALS	1.26 (1.23 to 1.3)	1.29 (1.25 to 1.33)	1.23 (1.18 to 1.27)	1.17 (1.14 to 1.2)	1.39 (1.23 to 1.56)
AIS	1.3 (1.26 to 1.34)	1.33 (1.29 to 1.38)	1.23 (1.17 to 1.29)	1.23 (1.19 to 1.27)	1.52 (1.35 to 1.72)
AEC	1.31 (1.27 to 1.35)	1.34 (1.29 to 1.39)	1.25 (1.19 to 1.31)	1.22 (1.18 to 1.27)	1.65 (1.47 to 1.86)
ACOB	1.33 (1.3 to 1.36)	1.35 (1.32 to 1.39)	1.32 (1.28 to 1.36)	1.2 (1.17 to 1.23)	1.47 (1.33 to 1.63)
ADS	1.33 (1.31 to 1.36)	1.38 (1.34 to 1.41)	1.31 (1.26 to 1.35)	1.21 (1.18 to 1.24)	1.45 (1.31 to 1.61)

Model 2 - adjusted for age, sex, socioeconomic status, BMI, smoking, alchohol and phyiscal activity

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
ARS	1.14 (1.1 to 1.18)	1.14 (1.09 to 1.19)	1.1 (1.04 to 1.16)	1.09 (1.05 to 1.14)	1.33 (1.12 to 1.58)
CrAS	1.15 (1.11 to 1.18)	1.17 (1.13 to 1.21)	1.1 (1.05 to 1.15)	1.12 (1.09 to 1.16)	1.31 (1.15 to 1.5)
m-ARS	1.15 (1.12 to 1.19)	1.17 (1.12 to 1.21)	1.1 (1.05 to 1.16)	1.12 (1.08 to 1.16)	1.38 (1.2 to 1.58)
AAS-r	1.16 (1.12 to 1.19)	1.19 (1.15 to 1.22)	1.13 (1.09 to 1.18)	1.13 (1.1 to 1.17)	1.25 (1.09 to 1.43)
ALS	1.16 (1.13 to 1.2)	1.19 (1.15 to 1.23)	1.11 (1.07 to 1.16)	1.14 (1.11 to 1.18)	1.36 (1.2 to 1.55)
AAS	1.17 (1.14 to 1.2)	1.2 (1.16 to 1.24)	1.14 (1.09 to 1.18)	1.13 (1.1 to 1.16)	1.36 (1.2 to 1.53)
AIS	1.19 (1.15 to 1.23)	1.23 (1.18 to 1.28)	1.12 (1.06 to 1.18)	1.19 (1.15 to 1.23)	1.48 (1.29 to 1.7)
AEC	1.2 (1.15 to 1.24)	1.22 (1.17 to 1.28)	1.13 (1.07 to 1.2)	1.18 (1.14 to 1.22)	1.59 (1.4 to 1.81)
ACOB	1.23 (1.2 to 1.26)	1.26 (1.22 to 1.3)	1.21 (1.17 to 1.26)	1.16 (1.13 to 1.2)	1.42 (1.27 to 1.59)
ADS	1.23 (1.2 to 1.26)	1.27 (1.24 to 1.31)	1.19 (1.15 to 1.24)	1.18 (1.14 to 1.21)	1.43 (1.28 to 1.6)

Model 3 - adjuted for age, sex, socioeconomic status, BMI, smoking, alchohol, physical activity and number of long-term conditions

scales	MACE/mortality	All-cause mortality	MACE	Fall or fracture	Dementia/delirium
CrAS	1.03 (1 to 1.07)	1.05 (1.01 to 1.09)	0.99 (0.94 to 1.04)	1.06 (1.03 to 1.1)	1.22 (1.05 to 1.41)
ALS	1.04 (1 to 1.07)	1.06 (1.02 to 1.1)	0.99 (0.94 to 1.03)	1.08 (1.04 to 1.11)	1.26 (1.09 to 1.46)
ARS	1.04 (1 to 1.08)	1.03 (0.98 to 1.08)	1 (0.95 to 1.06)	1.04 (0.99 to 1.08)	1.23 (1.03 to 1.48)
m-ARS	1.05 (1.01 to 1.08)	1.05 (1 to 1.09)	1 (0.95 to 1.06)	1.06 (1.02 to 1.1)	1.28 (1.1 to 1.49)
AAS-r	1.05 (1.02 to 1.08)	1.08 (1.04 to 1.11)	1.03 (0.99 to 1.07)	1.08 (1.05 to 1.11)	1.13 (0.97 to 1.32)
AAS	1.05 (1.02 to 1.09)	1.08 (1.04 to 1.12)	1.02 (0.98 to 1.07)	1.07 (1.04 to 1.1)	1.25 (1.09 to 1.44)
AEC	1.08 (1.04 to 1.12)	1.1 (1.05 to 1.15)	1.02 (0.96 to 1.08)	1.11 (1.07 to 1.16)	1.5 (1.3 to 1.72)
AIS	1.08 (1.04 to 1.12)	1.1 (1.06 to 1.15)	1 (0.95 to 1.06)	1.12 (1.08 to 1.17)	1.38 (1.19 to 1.61)
ACOB	1.12 (1.09 to 1.15)	1.14 (1.1 to 1.18)	1.11 (1.06 to 1.15)	1.1 (1.07 to 1.14)	1.33 (1.17 to 1.51)
ADS	1.12 (1.09 to 1.15)	1.16 (1.12 to 1.2)	1.08 (1.04 to 1.13)	1.12 (1.08 to 1.15)	1.34 (1.17 to 1.52)

Sensitivity analysis 3: Model adjusted for all covariates of model 2 plus hypertension, coronary heart disease, diabetes, previous stroke/transient ischaemic attack, and heart failure at baseline, instead of adjusting for morbidity count. For primary outcome (cardiovascular event or death), all-cause mortality, and MACE

Hazard ratios per one-point increase in scale

scales	MACE/mortality	All-cause mortality	MACE
CrAS	1.1 (1.09 to 1.12)	1.11 (1.09 to 1.13)	1.06 (1.03 to 1.09)
ARS	1.11 (1.09 to 1.14)	1.12 (1.1 to 1.14)	1.07 (1.03 to 1.11)
AAS	1.11 (1.1 to 1.13)	1.12 (1.1 to 1.14)	1.1 (1.08 to 1.13)
AAS-r	1.11 (1.1 to 1.13)	1.12 (1.11 to 1.14)	1.11 (1.09 to 1.14)
ALS	1.12 (1.1 to 1.13)	1.13 (1.11 to 1.14)	1.09 (1.06 to 1.12)
m-ARS	1.14 (1.12 to 1.16)	1.15 (1.13 to 1.17)	1.09 (1.05 to 1.12)
AEC	1.15 (1.13 to 1.17)	1.16 (1.13 to 1.18)	1.11 (1.08 to 1.15)
AIS	1.15 (1.13 to 1.17)	1.16 (1.14 to 1.18)	1.11 (1.08 to 1.15)
ACOB	1.16 (1.14 to 1.18)	1.17 (1.16 to 1.19)	1.17 (1.14 to 1.2)
ADS	1.17 (1.16 to 1.19)	1.19 (1.17 to 1.2)	1.17 (1.14 to 1.2)

Post-hoc analyses:

Excluding participants with a prior history of fall or fracture

scales	Fall/fracture
CrAS	1.09 (1.05-1.12)
ARS	1.06 (1.02-1.1)
AAS	1.09 (1.06-1.12)
AAS-r	1.09 (1.06-1.12)
ALS	1.1 (1.07-1.14)
m-ARS	1.08 (1.04-1.12)
AEC	1.13 (1.09-1.17)
AIS	1.13 (1.1-1.17)
ACOB	1.11 (1.08-1.14)
ADS	1.12 (1.09-1.15)

Delirium as outcome, including participants with dementia at baseline

scales	Delirium
CrAS	1.09 (1.05-1.14)
ARS	1.12 (1.07-1.18)
AAS	1.10 (1.06-1.14)

AAS-r	1.14 (1.10-1.18)
ALS	1.11 (1.06-1.16)
m-ARS	1.15 (1.10-1.20)
AEC	1.20 (1.14-1.26)
AIS	1.20 (1.15-1.25)
ACOB	1.12 (1.07-1.16)
ADS	1.12 (1.07-1.16)

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Scales treated as categorical variables (score 1-2, and score ≥3)

The main analysis assessed the hazard ratio associated with one-point increase in each scale. We also analysed each scale as a categorical variable, the results of which are shown below. There is no generally accepted convention or cut-offs used to categorise anticholinergic scales. For consistency, we applied the same cut-offs to each scale:

- Score 1 – 2 (low)
- Score 3 or more

A score of 0 was the reference group

Hazard ratio for categorised scales

Model 1 - Adjusted for age, sex, and socioeconomic status

Primary outcome (MACE or death)

scales	Score 1 to 2	Score 3 or more
AAS	1.83 (1.76 to 1.9)	2.17 (2.04 to 2.31)
AAS-r	1.88 (1.8 to 1.97)	2.08 (1.96 to 2.21)
ACOB	1.8 (1.73 to 1.87)	2.36 (2.23 to 2.49)
ADS	1.89 (1.82 to 1.96)	2.55 (2.42 to 2.69)
AEC	1.89 (1.79 to 1.98)	1.96 (1.83 to 2.1)
AIS	1.88 (1.78 to 1.97)	2.01 (1.89 to 2.14)
ALS	1.68 (1.62 to 1.74)	2.15 (2.03 to 2.28)
ARS	1.52 (1.43 to 1.61)	1.88 (1.75 to 2.01)
CrAS	1.54 (1.48 to 1.6)	2.04 (1.92 to 2.16)
m-ARS	1.66 (1.58 to 1.74)	1.99 (1.86 to 2.12)

All-cause mortality

scales	Score 1 to 2	Score 3 or more
AAS	1.85 (1.78 to 1.93)	2.21 (2.07 to 2.36)
AAS-r	1.93 (1.84 to 2.02)	2.11 (1.98 to 2.26)
ACOB	1.82 (1.75 to 1.9)	2.43 (2.29 to 2.57)
ADS	1.93 (1.86 to 2.01)	2.64 (2.49 to 2.79)
AEC	1.92 (1.82 to 2.02)	2.01 (1.87 to 2.16)
AIS	1.94 (1.84 to 2.04)	2.06 (1.93 to 2.2)
ALS	1.71 (1.65 to 1.78)	2.19 (2.06 to 2.33)
ARS	1.52 (1.43 to 1.62)	1.91 (1.77 to 2.05)
CrAS	1.56 (1.5 to 1.63)	2.06 (1.93 to 2.19)
m-ARS	1.68 (1.59 to 1.77)	2.03 (1.9 to 2.18)

MACE

scales	Score 1 to 2	Score 3 or more
AAS	2.34 (2.19 to 2.5)	2.69 (2.41 to 3)
AAS-r	2.39 (2.22 to 2.58)	2.59 (2.32 to 2.88)
ACOB	2.34 (2.19 to 2.5)	3.21 (2.92 to 3.52)
ADS	2.21 (2.07 to 2.37)	3.38 (3.08 to 3.7)
AEC	2.11 (1.92 to 2.31)	2.01 (1.77 to 2.29)
AIS	1.99 (1.81 to 2.18)	2.07 (1.84 to 2.32)
ALS	1.91 (1.79 to 2.05)	2.48 (2.22 to 2.76)
ARS	1.52 (1.37 to 1.69)	1.9 (1.67 to 2.17)

CrAS	1.73 (1.61 to 1.85)	2.26 (2.02 to 2.51)
m-ARS	1.62 (1.47 to 1.78)	1.99 (1.76 to 2.25)

Fall or fracture

scales	Score 1 to 2	Score 3 or more
AAS	1.55 (1.45 to 1.67)	1.77 (1.59 to 1.97)
AAS-r	1.63 (1.51 to 1.76)	1.78 (1.6 to 1.98)
ACOB	1.5 (1.4 to 1.61)	1.83 (1.66 to 2.01)
ADS	1.72 (1.61 to 1.84)	1.9 (1.72 to 2.1)
AEC	1.88 (1.73 to 2.04)	1.69 (1.5 to 1.9)
AIS	1.93 (1.78 to 2.1)	1.75 (1.57 to 1.96)
ALS	1.59 (1.49 to 1.7)	1.71 (1.54 to 1.9)
ARS	1.39 (1.26 to 1.54)	1.55 (1.37 to 1.75)
CrAS	1.49 (1.39 to 1.59)	1.67 (1.51 to 1.86)
m-ARS	1.45 (1.32 to 1.58)	1.63 (1.45 to 1.83)

Dementia or delirium

scales	Score 1 to 2	Score 3 or more
AAS	2.38 (1.71 to 3.29)	4.46 (2.95 to 6.73)
AAS-r	2.03 (1.4 to 2.93)	3.24 (2.08 to 5.04)
ACOB	2.08 (1.51 to 2.86)	3.29 (2.17 to 5.01)
ADS	2.24 (1.62 to 3.1)	4.1 (2.77 to 6.07)
AEC	4.64 (3.31 to 6.52)	4.42 (2.81 to 6.94)
AIS	4.93 (3.52 to 6.9)	3.97 (2.57 to 6.14)
ALS	2.13 (1.55 to 2.93)	4.27 (2.84 to 6.42)
ARS	2.36 (1.55 to 3.59)	2.52 (1.48 to 4.28)
CrAS	2.2 (1.61 to 3.02)	3.63 (2.37 to 5.55)
m-ARS	3.02 (2.11 to 4.33)	2.63 (1.57 to 4.42)

Model 2 - Adjusted for age, sex, socioeconomic status, BMI, smoking, alcohol and physical activity

Primary outcome (MACE or death)

scales	Score 1 to 2	Score 3 or more
AAS	1.59 (1.53 to 1.66)	1.67 (1.57 to 1.79)
AAS-r	1.64 (1.56 to 1.71)	1.61 (1.51 to 1.72)
ACOB	1.59 (1.53 to 1.65)	1.86 (1.75 to 1.97)
ADS	1.64 (1.57 to 1.71)	1.98 (1.86 to 2.09)
AEC	1.63 (1.54 to 1.72)	1.5 (1.39 to 1.61)
AIS	1.6 (1.51 to 1.69)	1.59 (1.48 to 1.7)
ALS	1.46 (1.4 to 1.52)	1.65 (1.55 to 1.77)
ARS	1.36 (1.28 to 1.44)	1.47 (1.36 to 1.59)
CrAS	1.37 (1.31 to 1.42)	1.6 (1.51 to 1.71)
m-ARS	1.45 (1.37 to 1.53)	1.56 (1.46 to 1.68)

All-cause mortality

scales	Score 1 to 2	Score 3 or more
AAS	1.62 (1.55 to 1.7)	1.7 (1.59 to 1.83)
AAS-r	1.68 (1.61 to 1.77)	1.64 (1.53 to 1.76)
ACOB	1.61 (1.54 to 1.68)	1.91 (1.8 to 2.03)
ADS	1.68 (1.61 to 1.75)	2.05 (1.93 to 2.18)
AEC	1.65 (1.56 to 1.75)	1.54 (1.42 to 1.66)
AIS	1.64 (1.55 to 1.74)	1.62 (1.51 to 1.74)
ALS	1.5 (1.43 to 1.56)	1.68 (1.57 to 1.8)
ARS	1.37 (1.28 to 1.46)	1.49 (1.38 to 1.62)

CrAS	1.39 (1.33 to 1.45)	1.62 (1.52 to 1.74)
m-ARS	1.47 (1.39 to 1.55)	1.6 (1.48 to 1.72)

MACE

scales	Score 1 to 2	Score 3 or more
AAS	1.9 (1.77 to 2.05)	1.91 (1.69 to 2.14)
AAS-r	1.97 (1.82 to 2.14)	1.84 (1.64 to 2.07)
ACOB	1.96 (1.83 to 2.11)	2.35 (2.12 to 2.6)
ADS	1.84 (1.71 to 1.98)	2.41 (2.18 to 2.67)
AEC	1.75 (1.59 to 1.93)	1.41 (1.23 to 1.63)
AIS	1.62 (1.46 to 1.79)	1.49 (1.31 to 1.7)
ALS	1.55 (1.44 to 1.66)	1.73 (1.54 to 1.95)
ARS	1.32 (1.18 to 1.47)	1.37 (1.19 to 1.58)
CrAS	1.44 (1.33 to 1.54)	1.63 (1.45 to 1.84)
m-ARS	1.37 (1.24 to 1.51)	1.43 (1.25 to 1.64)

Fall or fracture

scales	Score 1 to 2	Score 3 or more
AAS	1.51 (1.4 to 1.63)	1.59 (1.41 to 1.79)
AAS-r	1.53 (1.41 to 1.67)	1.61 (1.44 to 1.81)
ACOB	1.46 (1.35 to 1.57)	1.63 (1.46 to 1.81)
ADS	1.67 (1.56 to 1.79)	1.68 (1.51 to 1.88)
AEC	1.78 (1.63 to 1.94)	1.49 (1.3 to 1.69)
AIS	1.82 (1.67 to 1.98)	1.59 (1.41 to 1.79)
ALS	1.57 (1.46 to 1.68)	1.56 (1.39 to 1.76)
ARS	1.37 (1.24 to 1.52)	1.37 (1.2 to 1.56)
CrAS	1.46 (1.36 to 1.56)	1.53 (1.37 to 1.72)
m-ARS	1.41 (1.28 to 1.55)	1.45 (1.28 to 1.65)

Dementia or delirium

scales	Score 1 to 2	Score 3 or more
AAS	2.2 (1.54 to 3.15)	3.91 (2.48 to 6.16)
AAS-r	1.85 (1.24 to 2.78)	3.03 (1.89 to 4.86)
ACOB	1.98 (1.4 to 2.8)	2.88 (1.81 to 4.57)
ADS	2.16 (1.52 to 3.07)	3.9 (2.55 to 5.98)
AEC	4.28 (2.96 to 6.19)	4.15 (2.56 to 6.74)
AIS	4.6 (3.19 to 6.64)	4.04 (2.56 to 6.38)
ALS	2.01 (1.42 to 2.84)	3.99 (2.55 to 6.22)
ARS	2.19 (1.4 to 3.44)	2.21 (1.24 to 3.93)
CrAS	2.17 (1.55 to 3.05)	3.53 (2.24 to 5.57)
m-ARS	2.96 (2.02 to 4.33)	2.37 (1.35 to 4.14)

Model 3 - Adjusted for age, sex, socioeconomic status, BMI, smoking, alcohol, physical activity and number of long-term conditions

Primary outcome (MACE or death)

scales	Score 1 to 2	Score 3 or more
AAS	1.28 (1.22 to 1.34)	1.24 (1.16 to 1.33)
AAS-r	1.32 (1.26 to 1.39)	1.22 (1.14 to 1.31)
ACOB	1.32 (1.27 to 1.38)	1.44 (1.35 to 1.53)
ADS	1.36 (1.3 to 1.42)	1.52 (1.43 to 1.62)
AEC	1.29 (1.22 to 1.36)	1.18 (1.09 to 1.27)
AIS	1.26 (1.19 to 1.33)	1.25 (1.17 to 1.34)
ALS	1.18 (1.13 to 1.23)	1.22 (1.14 to 1.31)
ARS	1.13 (1.06 to 1.2)	1.17 (1.08 to 1.26)

CrAS	1.13 (1.08 to 1.18)	1.21 (1.13 to 1.29)
m-ARS	1.19 (1.13 to 1.26)	1.22 (1.14 to 1.32)

523 All-cause mortality

scales	Score 1 to 2	Score 3 or more
AAS	1.3 (1.24 to 1.36)	1.25 (1.16 to 1.35)
AAS-r	1.35 (1.28 to 1.42)	1.24 (1.15 to 1.33)
ACOB	1.34 (1.28 to 1.4)	1.47 (1.38 to 1.57)
ADS	1.39 (1.33 to 1.46)	1.57 (1.47 to 1.68)
AEC	1.3 (1.22 to 1.38)	1.2 (1.11 to 1.3)
AIS	1.29 (1.22 to 1.37)	1.27 (1.18 to 1.37)
ALS	1.21 (1.15 to 1.26)	1.23 (1.15 to 1.33)
ARS	1.13 (1.05 to 1.2)	1.18 (1.09 to 1.28)
CrAS	1.15 (1.1 to 1.2)	1.21 (1.13 to 1.3)
m-ARS	1.2 (1.13 to 1.27)	1.24 (1.15 to 1.34)

524 MACE

scales	Score 1 to 2	Score 3 or more
AAS	1.47 (1.36 to 1.59)	1.32 (1.16 to 1.49)
AAS-r	1.52 (1.4 to 1.66)	1.32 (1.17 to 1.49)
ACOB	1.6 (1.48 to 1.72)	1.74 (1.56 to 1.94)
ADS	1.47 (1.36 to 1.59)	1.75 (1.57 to 1.95)
AEC	1.3 (1.17 to 1.43)	1.04 (0.9 to 1.2)
AIS	1.19 (1.07 to 1.32)	1.09 (0.96 to 1.25)
ALS	1.18 (1.1 to 1.28)	1.16 (1.02 to 1.32)
ARS	1.04 (0.93 to 1.17)	1.02 (0.88 to 1.18)
CrAS	1.14 (1.05 to 1.23)	1.13 (1 to 1.27)
m-ARS	1.06 (0.96 to 1.17)	1.04 (0.9 to 1.19)

525 Fall or fracture

scales	Score 1 to 2	Score 3 or more
AAS	1.31 (1.21 to 1.42)	1.31 (1.16 to 1.49)
AAS-r	1.33 (1.22 to 1.45)	1.35 (1.2 to 1.53)
ACOB	1.29 (1.19 to 1.39)	1.38 (1.23 to 1.54)
ADS	1.48 (1.38 to 1.6)	1.44 (1.29 to 1.62)
AEC	1.53 (1.4 to 1.68)	1.28 (1.12 to 1.47)
AIS	1.58 (1.44 to 1.73)	1.37 (1.21 to 1.55)
ALS	1.38 (1.28 to 1.48)	1.32 (1.17 to 1.49)
ARS	1.21 (1.09 to 1.35)	1.17 (1.02 to 1.34)
CrAS	1.29 (1.2 to 1.39)	1.29 (1.14 to 1.45)
m-ARS	1.23 (1.12 to 1.36)	1.23 (1.08 to 1.4)

526 Dementia or delirium

scales	Score 1 to 2	Score 3 or more
AAS	1.72 (1.18 to 2.51)	2.65 (1.61 to 4.35)
AAS-r	1.4 (0.92 to 2.13)	2.01 (1.21 to 3.35)
ACOB	1.53 (1.07 to 2.2)	2.05 (1.25 to 3.35)
ADS	1.73 (1.2 to 2.5)	2.75 (1.73 to 4.38)
AEC	3.33 (2.25 to 4.93)	3.3 (2 to 5.45)
AIS	3.6 (2.44 to 5.32)	3.26 (2.03 to 5.24)
ALS	1.56 (1.08 to 2.26)	2.86 (1.78 to 4.62)
ARS	1.75 (1.1 to 2.77)	1.66 (0.92 to 2.98)
CrAS	1.74 (1.22 to 2.48)	2.59 (1.6 to 4.19)
m-ARS	2.38 (1.6 to 3.52)	1.79 (1.01 to 3.17)

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528 **Categorisation of Long-Term Conditions**

Morbidity grouping*	Conditions included
Hypertension	Hypertension Essential hypertension
Coronary heart disease	Heart attack/MI Angina
Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
Atrial fibrillation	Atrial fibrillation
Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
COPD	COPD/Chronic obstructive pulmonary disease Emphysema/Chronic bronchitis Emphysema
Asthma	Asthma
Bronchiectasis	Bronchiectasis
Cancer	“yes”/”no” to “have you ever had cancer?”
Dyspepsia	Gastro-oesophageal reflux (GORD) Oesophagitis/Barrett’s oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
Diverticular disease	Diverticular disease/diverticulitis
Irritable bowel syndrome	Irritable bowel syndrome
Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
Inflammatory bowel disease	Inflammatory bowel disease Crohn’s disease Ulcerative colitis

Constipation	Constipation
Viral hepatitis	Hepatitis B Hepatitis C Hepatitis D
Depression	Depression Postnatal depression
Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem
Schizophrenia/Bipolar affective disorder **Bipolar**	Scizophrenia Mania Bipolar disorder Manic depression
Connective tissue diseases	Myositis/myopathy Systemic lupus erythematosus/SLE Connective tissue disorder Sjogren's syndrome.sicca syndrome Dermatopolymyositis Scloeroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia rheumatica
Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Osteoporosis	Osteoporosis
Thyroid disorders	Thyroid problem (not cancer Hyperthroidism/thyrotoxicosis

	Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroititis
Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy
Glaucoma	Glaucoma
Epilepsy	Epilepsy
Dementia	Dementia/Alzheimer/cognitive impairment
Psoriasis or eczema	Eczema/dermatitis Psoriasis
Migraine	Migraine
Chronic sinusitis	Chronic sinusitis
Anorexia or bulimia	Anorexia, bulimia/other eating disorder
Parkinson's disease	Parkinson's disease
Multiple sclerosis	Multiple sclerosis
Chronic fatigue syndrome	Chronic fatigue syndrome
Endometriosis	Endometriosis
Meniere disease	Meniere disease
Pernicious anaemia	Pernicious anaemia
Polycystic ovaries	Polycystic ovaries
*Self-report lifetime diagnosis by doctor recorded by nurse-led interview (UK Biobank data field 20002), except cancer diagnosis which was reported by touch-screen questionnaire. The list of disease groupings was based on Barnett et al (2012)	

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Selection of anticholinergic scales

The identification of anticholinergic scales included in this analysis was based on searches for a systematic literature review (registered on PROSPERO: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017076510). The review itself is ongoing, and findings will be published elsewhere. Search strategy and identification of scales is summarized here briefly to explain the choice of scales included in this review.

Medline and Embase were searched up until September 2017 using the following terms:

anticholinergic*.mp or anti-cholinergic*.mp or cholinergic antagonist*.mp or antimuscarinic*.mp or anti-muscarinic*.mp or muscarinic antagonist*.mp
AND
scale*.mp or score*.mp or rank*.mp or rating*.mp or grading*.mp or index.mp or classification.mp

Titles and abstracts here screened by 2 reviewers to identify studies in which anticholinergic medication scales have been validated.

From 6558 abstracts screened, 377 full texts were identified as potentially relevant and screened for inclusion. From these, 14 anticholinergic scales were identified.

Of these 14 scales, 4 were excluded from this UK Biobank analysis:

- Summers' list (Summers 1978): This was not specifically an anticholinergic scale, and also was likely to exclude many more recent medications.
- Ancelin 2006: This was not a scale constructed for this study, but rather the application of an existing scale to a new cohort of patients. Only those medication found in the cohort were listed in the paper, hence we could not re-create the full scale from this text.
- Ellett 2014: This paper listed anticholinergic medication identified from a range of existing scales (all of which were included in our analysis). Medications scoring "1" were also excluded. This was therefore not a distinct anticholinergic scale, rather a collection of medicaitons from existing scales already included in our analysis.
- MARANTE (Klamer 2017): This scale was based on daily dosage calculations. As UK Biobank did not collect data on medication dosage we were unable to include this scale.

This left 10 anticholinergic scales which were included in our analysis: Anticholinergic Drug Scale (ADS),[8] Clinician-rated Anticholinergic Scale (CrAS),[5] Anticholinergic Risk Scale (ARS),[4] Anticholinergic Cognitive Burden (ACoB),[3] Anticholinergic Activity Scale (AAS),[6] revised Anticholinergic Activity Scale

(AAS-r),[7] Anticholinergic Loading Scale (ALS),[9] Modified Anticholinergic Risk Scale (m-ARS),[12] Anticholinergic Effect on Cognition (AEC),[10] Anticholinergic Impregnation Scale (AIS).[11]

579 **Anticholinergic medications and their classification according to each anticholinergic medication**
580 **scale.**

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Medication	AIS	AEC	mARS	ACoB	AAS (Chew)	ALS	AAS (Ehrt)†	CrAS	ARS	ADS
Alimemazine	1	3		1						
Alprazolam	1			1		1		1		1
Alverine	1			1						
Amantadine	2	2	2	2					2	1
Amiodarone		1								
Amitriptyline	3	3	3	3	3	3	3	3	3	3
Amoxapine	3			3						
Ampicillin	1									1
Aripiprazole		1								
Atenolol	1			1				1		
Atropine	3	3	3	3	3	3		3	3	3
Azathioprine	1									1
Baclofen	2		2					2	2	
Belladonna				2				3		
Benazepril								1		
Benztropine		3	3	3			3		3	3
Betaxolol								1		
Biperiden	3									
Bisacodyl						1				
Bromocriptine	1	1								1
Brompheniramine	3			3						3

Bupropion	1			1				1		
Captopril	1			1						1
Carbamazepine	2	1		2				1		2
Carbidopa ± levodopa	1		1			1		1	1	
Carbinoxamine				3						3
Carisoprodol									3	
Cefamandole										1
Cefoxitin	1									1
Celecoxib						1				
Cephalothin										1
Cetirizine	2		2			2		2	2	
Chlordiazepoxide	1							1		1
Chlorphenamine	3	2	3	3		3		3	3	3
Chlorpromazine	3	3	3	3	2			3	3	3
Chlorthalidone	1			1						1
Cimeditine	2		2	1					2	2
Citalopram	1	1			1	1	1			
Clemastine		3	3	3						3
Clindamycin	1									1
Clomipramine	3	3	2	3						3
Clonazepam	1					1				1
Clorazepate	1			1						1
Clozapine	3	3	2	3	3		3		2	3
Co-codamol				2						
Codeine	1			1		1		1		1
Colchicine	1			1						

Cortisone										1
Cyamemazine	3									
Cyclobenzaprine				2				1	2	2
Cycloserine										1
Cyclosporine	1									1
Cyproheptadine	3	3	3	2		3			3	2
Darifenacin			2	3						3
Desipramine		2	2	3				2	2	3
Desloratadine	3									
Dexamethasone	1									1
Dexchlorpheniramine	3					3				
Dextromethorphan								1		
Diazepam	1	1		1		1	1	1		1
Dicycloverine/dicyclomine		2	3	3	3				3	3
Digitoxin							1			1
Digoxin	1			1		1	1			1
Diltiazem	1									1
Dimenhydrinate	3	2		3						3
Diphenhydramine	3	2		3	2			3	3	3
Dipyridamole				1						1
Disopyramide	2	2		1						2
Divalproex sodium	1									1
Domperidone	1	1				1				

Dothiepin/dosulepin	2	3	2			2				
Doxepin	3	3	2	3	3	3	3	3		3
Doxylamine	2									
Duloxetine	1									
Emepronium							3			
Entacapone	1		1						1	
Escitalopram					1	1				
Estazolam										1
Famotidine	1									1
Fentanyl	1	1		1						1
Fesoterodine			2							
Fexofenadine	2					2		2		
Flavoxate	3		2	3						3
Flunitrazepam							1			
Fluoxetine	1	1			1	1	1	1		1
Fluphenazine	3	1	3			3			3	1
Flurazepam										1
Fluticasone-salmeterol										1
Fluvoxamine	1			1		1	1			1
Furosemide				1			1			1
Gentamicin	1									1
Guaifenesin								1		
Haloperidol	1		1	1		2			1	
Homatropine								3		
Hydralazine				1						1

Hydrocodone/dihydrocodeinone								2		
Hydrocortisone	1			1						1
Hydroxyzine	3	1	3	3					3	3
Hyoscine/scopolamine	3	3		3				3		3
Hyoscyamine/L-hyoscyamine			3	3	3				3	3
Iloperidone		1								
Imipramine	3	3	3	3		3		3	3	3
Ipratropium	3						3			
Isosorbide	1			1						1
Isosorbide dinitrate										1
Isosorbide mononitrate										1
Ketorolac								1		
Ketotifen*										1
Lansoprazole							1			
Levodopa	1									
Levomepromazine/methotrimeprazine	2	2	2	2						2
Lithium	1	1			1	1				
Lofepramine		3	1							
Loperamide	2		2	1		1		1	2	1
Loratadine	2		2			1		1	2	
Lorazepam	1									1
Loxapine	2			2						2

Lumiracoxib						1				
Maprotiline	3									
Meclozine/meclizine				3					3	3
Meperidine/pethidine	2	2		2						2
Mequitazine	3									
Metformin						1				
Methadone	2							2		
Methocarbamol	1		1					1	1	
Methotrexate						1				
Methylprednisolone	1									1
Metoclopramide/ Reglan	1		1			1		3	1	
Metoprolol	1			1				1		
Midazolam	1									1
Mirtazapine	1	1	1		1				1	
Molindone				2						2
Morphine	1			1				1		1
Naratriptan						1				
Nefazodone								1		
Nifedipine	1			1						1
Nizatidine	1									1
Nortriptyline	3	3	2	3	2		2	3	2	3
Olanzapine	2	2	2	3	2		2	1	2	1
Orphenadrine		3	3	3			3			3
Oxazepam	1					1				1

Oxcarbazepine	2			2						2
Oxybutynin	3	3	3	3	2	2	3		3	3
Oxycodone	1					1		1		1
Pancuronium										1
Paroxetine	2	2	1	3	2	2	2	2	1	1
Perphenazine	3	1	3	3				2	3	1
Phenelzine	1									1
Phenobarbital							1	1		
Pimozide	2	2		2						2
Piperacillin	1									1
Pipotiazine	1									
Pramipexole	1		1						1	
Prednisolone	1	1								1
Prednisone	1			1						1
Prochlorperazine	2	2	2			2		2	2	1
Procyclidine		3	3	3						3
Promazine		2		3			2			
Promethazine	3	3	3	3					3	3
Propantheline		2		3				2		3
Propericiazine/pericyazine	1		2							
Propiverine			2							
Propoxyphene							1	2		
Protriptyline						3				3
Pseudoephedrine ± triprolidine	2		2			2			2	
Pyrilamine/mepryamine				3						3

Quetiapine	2	2	1	3	1		1	2	1	
Quinidine	1	1		1						
Ranitidine	1		1	1	1	1	1	2	1	2
Reboxetine			1							
Risperidone	1		1	1		1		1	1	
Robitussin								1		
Selegiline	1		1						1	
Sertindole		1								
Sertraline	1	1						1		1
Solifenacin	3	1	2							
Sumatriptan						1				
Temazepam	1	1			1	1				1
Theophylline	1			1		2	1			1
Thioridazine			3	3	3		3	3	3	3
Thiothixine									3	1
Tiotropium			2							
Tizanidine	3		3						3	
Tolterodine	3	2	2	3	3	3		3	2	3
Tramadol	1					2		2		1
Trandolapril								1		
Trazodone	1		1	1				1	1	
Triamcinolone	1									1
Triamterene	1			1						1
Triazolam								1		1
Trifluoperazine		2	3	3					3	1
Trihexyphenidyl/ Benzhexol	3	3		3			3	3		3

Trimipramine	3	3	2	3			3			3
Triprolidine	2									
Tropatepine	3									
Trospium	3		2							
Valproic acid	1									1
Vancomycin	1									1
Venlafaxine						1		1		
Warfarin	1			1						1
Ziprasidone									1	
Zolmitriptan						1				

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586 *Ophthalmic preparation.

587 †Original 4-point scale modified by combining scores '1' or '2' to score as '1', scoring '3' as '2', and
588 '4' as '3' to fit the 3-point scale system of other scales.

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